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ORIGINAL ARTICLE

Development of Lifetime Comorbidity in the World Health Organization World Mental Health Surveys

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Context: Although numerous studies have examined the role of latent variables in the structure of comorbidity among mental disorders, none has examined their role in the development of comorbidity.

Objective: To study the role of latent variables in the development of comorbidity among 18 lifetime *DSM-IV* disorders in the World Health Organization World Mental Health Surveys.

Design: Nationally or regionally representative community surveys.

Setting: Fourteen countries.

Participants: A total of 21 229 survey respondents.

Main Outcome Measures: First onset of 18 lifetime *DSM-IV* anxiety, mood, behavior, and substance disorders assessed retrospectively in the World Health Organization Composite International Diagnostic Interview.

Results: Separate internalizing (anxiety and mood disorders) and externalizing (behavior and substance disorders) factors were found in exploratory factor analysis of lifetime disorders. Consistently significant positive time-lagged associations were found in survival analyses for virtually all temporally primary lifetime disorders predicting subsequent onset of other disorders. Within-domain (ie, internalizing or externalizing) associations were generally stronger than between-domain associations. Most time-lagged associations were explained by a model that assumed the existence of mediating latent internalizing and externalizing variables. Specific phobia and obsessive-compulsive disorder (internalizing) and hyperactivity and oppositional defiant disorders (externalizing) were the most important predictors. A small number of residual associations remained significant after controlling the latent variables.

Conclusions: The good fit of the latent variable model suggests that common causal pathways account for most of the comorbidity among the disorders considered herein. These common pathways should be the focus of future research on the development of comorbidity, although several important pairwise associations that cannot be accounted for by latent variables also exist that warrant further focused study.

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COMORBIDITY IS THE NORM among common mental disorders because more than 50% of people with a mental disorder in a given year meet criteria for multiple disorders.[1,2] The structure of this comorbidity has been the subject of considerable interest. Beginning with an influential article by Krueger,[3] numerous researchers have documented that bivariate associations among hierarchy-free anxiety, mood, behavior, and substance disorders can be accounted for by correlated latent predispositions to internalizing and externalizing disorders, with division of internalizing disorders into secondary dimensions of fear (eg, panic and phobia) and distress (eg, major depressive episode and generalized anxiety disorder).[4-9]

For editorial comment see page 10

These results have been used to argue for a reorganization of the classification of mental disorders in the *DSM* and *International Classification of Disease* diagnostic systems.[10-13] However, additional work is needed to evaluate the empirical support for such a reorganization because the framework has only recently been expanded to include additional forms of psychopathology, such as psychotic experiences.[14] Moreover, additional research on the stability of

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the structure across sociodemographic variables (eg, age, sex, and education) would be informative.

These results have also been used occasionally to investigate whether risk factors for individual disorders are more accurately conceptualized as risk factors for the latent dimensions underlying these disorders. Kramer and colleagues,[15] for example, found that observed sex differences in several internalizing and externalizing disorders became statistically insignificant when controls were included for latent internalizing-externalizing dimensions. Such evidence can be valuable in distinguishing between specific and nonspecific risk factors. The use of latent variable models in this way is only in its infancy. One obvious application is to the development of comorbidity itself. In particular, although the cross-sectional structure of comorbidity has been examined in a number of studies, we are unaware of attempts to investigate the role of latent dimensions in accounting for the development of comorbidity.

Although several studies used longitudinal data to determine whether the structure of internalizing and externalizing disorders is stable over time,[9,16,17] none investigated whether this structure accounts for the associations between temporally primary disorders and the subsequent first onset of comorbid disorders. A number of other longitudinal studies examined temporal progression[18,19] or sequencing[20-23] between earlier and later mental disorders, documenting strong persistence of individual disorders over time and significant predictive associations between some but not other temporally primary and later disorders. For example, Fergusson and colleagues[18] found that childhood conduct disorder but not attention-deficit/hyperactivity disorder (ADHD) predicted subsequent substance disorders. None of these studies, however, investigated whether associations of earlier disorders with onset of later disorders were mediated by latent variables.

Analysis of the latter sort could be useful in identifying potentially modifiable risk pathways by focusing attention on subsets of disorders with especially strong predictive associations that could subsequently be examined in more focused analyses.[24,25] For example, clinical studies finding childhood impulse-control problems in a subset of patients with early-onset obsessive-compulsive disorder (OCD)[26,27] and finding that impulse-control disorders continue to feature prominently in some cases of adult OCD[28,29] have created interest in the importance of inhibitory dyscontrol in the pathogenesis of OCD.[30] However, the role of putative neurobiological markers of such dyscontrol in accounting for the associations of impulse-control disorders with subsequent OCD remains unstudied. The documentation in epidemiological data of special associations between a cluster of early-onset impulse-control disorders and subsequent OCD could help spur such research by suggesting that more focused prospective neurobiological studies of this cluster beginning in childhood might yield valuable information about an important OCD subtype.

The present report proposes a novel approach to investigate the role of latent variables in the development of comorbidity. We begin with a conventional survival analysis of epidemiological data collected in 14 countries in the World Health Organization (WHO) World Mental Health (WMH) Survey Initiative[31] to study associations between earlier lifetime disorders and the subsequent first onset of later disorders. We then elaborate these survival models using a new latent modeling approach to examine the extent to which the associations among observed disorders can be accounted for by the mediating effects of latent internalizing and externalizing variables.

METHODS

SAMPLES

The 14 WMH countries include 7 classified by the World Bank as developed (Belgium, France, Germany, Italy, the Netherlands, Spain, and the United States) and 7 classified as developing (Brazil, Colombia, India, Lebanon, Mexico, the Peoples' Republic of China, and Romania) (**Table 1**). Surveys were administered in multistage, clustered area probability household samples representative of specific regions within countries (Brazil, Colombia, India, Mexico, and the Peoples' Republic of China) or entire countries (the remaining countries). Respondents were interviewed face-to-face by trained lay interviewers who explained the purposes of the survey, made clear that participation was voluntary and that responses would be treated as confidential, and obtained informed consent before beginning interviews. These recruitment and consent procedures were approved by the local human subjects committee that monitored the study in each country. A total of 61 292 respondents were interviewed. Country-specific response rates ranged from 45.9% (France) to 98.6% (India). The weighted (by sample size) average response rate was 71.1%.

The interview was divided into 2 parts. Part 1 assessed core disorders and was completed by all respondents. Part 2 assessed additional disorders and numerous correlates and was completed by 100% of respondents who met criteria for any part 1 disorder plus a probability subsample of other part 1 respondents. Based on a concern about recall bias, disorders defined as beginning in childhood (ADHD, conduct disorder, oppositional defiant disorder [ODD], and separation anxiety disorder) were assessed only among respondents aged 18 to 44 years. This part 2 subsample, which ranges in size from 486 respondents in Belgium to 6218 in the Peoples' Republic of China and totals 21 229 respondents across countries, is the sample used in the present report. The part 1 samples were weighted to adjust for differential probabilities of selection and residual discrepancies between sample and census on sociodemographic and geographic variables. In addition, the part 2 samples were weighted to adjust for undersampling of part 1 respondents without part 1 disorders. A more detailed discussion of WMH sampling and weighting is presented elsewhere.[32]

DIAGNOSTIC ASSESSMENT

Diagnoses were based on version 3.0 of the WHO Composite International Diagnostic Interview (CIDI),[33] a fully structured, lay-administered interview that generates diagnoses according to *ICD-10* and *DSM-IV* criteria. The *DSM-IV* criteria are used herein. Translation and back-translation followed standard WHO procedures.[34] The 7-day interviewer training program was standardized across countries. Training culminated in an examination that had to be passed before the interviewer could begin production data collection. A more detailed discussion of WMH training and quality control is presented elsewhere.[35]

The 18 lifetime diagnoses include mood disorders (bipolar I-II or subthreshold disorder [BPD] and major depressive episode/dysthymia), anxiety disorders (agoraphobia with or without panic disorder, generalized anxiety disorder [GAD], OCD, panic disorder with or without agoraphobia, posttraumatic stress

Table 1. WMH Survey Sample Characteristics

Country	Survey[a]	Sample Design	Field Dates	Age Range, y	Sample Size			Response Rate, %[b]
					Part 1	Part 2	Part 2 and Aged 18-44 y[a]	
Developed Countries								
Belgium	ESEMeD	Stratified multistage clustered probability sample of individuals residing in households from the national register of Belgium residents; NR	2001-2002	≥18	2419	1043	486	50.6
France	ESEMeD	Stratified multistage clustered sample of working telephone numbers merged with a reverse directory (for listed numbers); initial recruitment was by telephone, with supplemental in-person recruitment in households with listed numbers; NR	2001-2002	≥18	2894	1436	727	45.9
Germany	ESEMeD	Stratified multistage clustered probability sample of individuals from community resident registries; NR	2002-2003	≥18	3555	1323	621	57.8
Italy	ESEMeD	Stratified multistage clustered probability sample of individuals from municipality resident registries; NR	2001-2002	≥18	4712	1779	853	71.3
The Netherlands	ESEMeD	Stratified multistage clustered probability sample of individuals residing in households listed in municipal postal registries; NR	2002-2003	≥18	2372	1094	516	56.4
Spain	ESEMeD	Stratified multistage clustered area probability sample of household residents; NR	2001-2002	≥18	5473	2121	960	78.6
United States	NCS-R	Stratified multistage clustered area probability sample of household residents; NR	2002-2003	≥18	9282	5692	3197	70.9
Total					**30 707**	**14 488**	**7360**	63.8
Developing Countries								
Brazil	São Paulo Megacity	Stratified multistage clustered area probability sample of household residents in the São Paulo metropolitan area	2004-2007	≥18	5037	2942	1824	81.3
Colombia	NSMH	Stratified multistage clustered area probability sample of household residents in all urban areas of the country (approximately 73% of the total national population)	2003	18-65	4426	2381	1731	87.7
India	WMHI	Stratified multistage clustered area probability sample of household residents in Pondicherry region; NR	2003-2005	≥18	2992	1373	825	98.6
Lebanon	LEBANON	Stratified multistage clustered area probability sample of household residents; NR	2002-2003	≥18	2857	1031	595	70.0
Mexico	M-NCS	Stratified multistage clustered area probability sample of household residents in all urban areas of the country (approximately 75% of the total national population)	2001-2002	18-65	5782	2362	1736	76.6
PRC	Shenzhen	Stratified multistage clustered area probability sample of household residents and temporary residents in the Shenzhen area	2006-2007	≥18	7134	7134[c]	6218[c]	80.0
Romania	RMHS	Stratified multistage clustered area probability sample of household residents; NR	2005-2006	≥18	2357	2357	940	70.9
Total					**30 585**	**19 580**	**13 869**	80.2
Total for All Countries					**61 292**	**34 068**	**21 229**	71.1

Abbreviations: ESEMeD, European Study of the Epidemiology of Mental Disorders; LEBANON, Lebanese Evaluation of the Burden of Ailments and Needs of the Nation; M-NCS, Mexico National Comorbidity Survey; NCS-R, US National Comorbidity Survey Replication; NR, nationally representative; NSMH, Colombian National Study of Mental Health; PRC, People's Republic of China; RMHS, Romania Mental Health Survey; WMH, World Mental Health; WMHI, WMH India.

[a] Most WMH surveys are based on stratified multistage clustered area probability household samples in which samples of areas equivalent to counties or municipalities in the United States were selected in the first stage followed by 1 or more subsequent stages of geographic sampling (eg, towns within counties, blocks within towns, households within blocks) to arrive at a sample of households, in each of which a listing of household members was created and 1 or 2 people were selected from this listing to be interviewed. No substitution was allowed when the originally sampled household resident could not be interviewed. These household samples were selected from census area data in all countries other than France (where telephone directories were used to select households) and the Netherlands (where postal registries were used to select households). Several WMH surveys (Belgium, Germany, and Italy) used municipal resident registries to select respondents without listing households. Ten of the 14 surveys are based on NR household samples. The others are representative of particular cities (Brazil and India) or the urbanized areas of the country (Colombia and Mexico).

[b] Calculated as the ratio of the number of households in which an interview was completed to the number of households originally sampled, excluding from the denominator households known not to be eligible because of being vacant at the time of initial contact or because the residents were unable to speak the designated languages of the survey.

[c] In Shenzhen, all respondents received the part 2 interview and all respondents aged 18 through 44 years were used in the current analysis.

disorder [PTSD], separation anxiety disorder, social phobia, and specific phobia), behavior disorders (attention-deficit disorder [ADD], hyperactivity disorder [HD], conduct disorder with covert symptoms [CD1; eg, lying, shoplifting], conduct disorder with overt symptoms [CD2; eg, bullying, being physically cruel to people], intermittent explosive disorder [IED], and

ODD), and substance disorders (alcohol and other drug abuse with or without dependence).

As detailed elsewhere,[36] blinded clinical reappraisal interviews found generally good concordance between *DSM-IV* diagnoses based on the CIDI and those based on the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[37] Organic exclusions but not diagnostic hierarchy rules were used in making diagnoses. The CIDI included retrospective disorder age-at-onset reports based on a special question sequence that has been shown experimentally to improve recall accuracy.[38] Respondents were asked to date their age when they first had the full syndrome for each disorder, not the first symptom of the disorder.

ANALYSIS METHODS

Exploratory principal axis tetrachoric factor analysis with promax rotation was used to examine bivariate comorbidity. Clear internalizing (10 disorders) and externalizing (8 disorders) dimensions were found but no evidence of a third factor that distinguished fear from distress disorders. Discrete-time survival analysis[39] with person-year as the unit of analysis and a logistic link function[40] was then used to study associations of temporally primary lifetime disorders with subsequent first onset of later disorders. Each model predicted first onset of 1 of the 18 *DSM-IV*/CIDI disorders from information about prior lifetime occurrence of the other 17 disorders ($18 \times 17 = 306$ pairwise associations), which were treated as time-varying covariates, controlling for respondent age, sex, and country. Retrospective age-at-onset reports were used to define the predictor disorders as time varying and to define age at onset of the outcome disorders.

We then estimated a latent variable model that constrained the coefficients in the observed variable models to be mediated by hypothesized continuous time-varying latent internalizing and externalizing variables. The coefficients in the observed variable model were constrained in the sense that this model included 306 coefficients (**Figure**, A), whereas the latent variable model used only 36 independent coefficients to reproduce these same associations (Figure, B). These included 10 coefficients (1 of which was nonindependent because the 10 coefficients together perfectly predict the time *t* latent variable) for the time *t* lifetime internalizing disorders predicting the time *t* latent internalizing variable; 8 coefficients (1 of which was nonindependent because the 8 coefficients together perfectly predict the time *t* latent variable) for the time *t* lifetime externalizing disorders predicting the time *t* latent externalizing variable; 4 coefficients (2 of which were nonindependent because the pair of time *t* latent variables perfectly predict each of the 2 time $t+1$ latent variables) for the time *t* latent internalizing and externalizing variables predicting the time $t+1$ latent internalizing and externalizing variables; 10 coefficients for the time $t+1$ latent internalizing variable predicting first onsets of the 10 time $t+1$ internalizing disorders; and 8 coefficients for the time $t+1$ latent externalizing variable predicting first onsets of the 8 time $t+1$ externalizing disorders.

In interpreting the latent variable results, it is useful to note that the latent variables are actually weighted (by odds ratios [ORs] of disorders predicting latent variables) composites of all predictor disorders. The assumption that a single weighted composite can represent the effects of all predictor disorders is equivalent to assuming that the ratios of the ORs across predictors are constant across outcomes. These constraints are the key features of the model. The standard covariance structure analysis programs used in previous studies of the structure of comorbidity could not be used to impose these constraints because discrete-time survival analysis is based on a person-year data array that varies in size across the outcomes. An iterative maximum-likelihood method implemented in a SAS macro was consequently written to estimate the coefficients.[41] This procedure sequentially estimated the

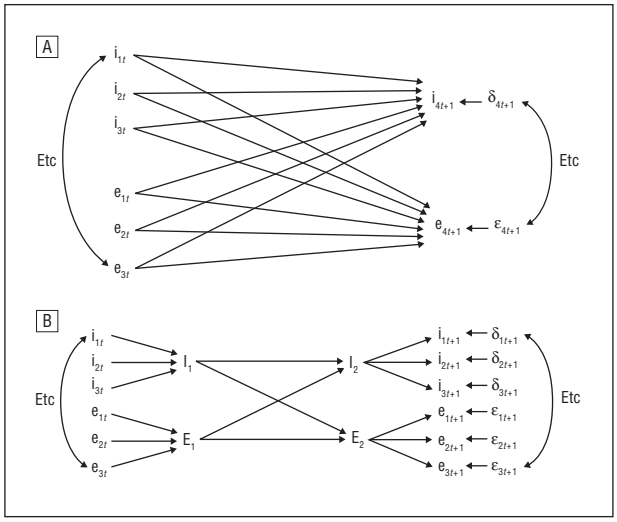

Figure. Model schematics. A, Schematic of the multivariate observed variable model. Only 3 observed lifetime time *t* internalizing disorders and externalizing disorders along with only 1 observed internalizing and 1 observed externalizing disorder at time $t+1$ are shown to simplify the presentation, but there were 10 observed lifetime internalizing and 8 observed externalizing disorders in the actual survival model at each time point. First onset of each of these 18 disorders between times *t* and $t+1$ was predicted by lifetime history of the other 17 disorders as of time *t*. Estimation was made in 18 separate survival equations, each with 17 predictors for history of the other disorders, for a total of 306 (18×17) pairwise time-lagged associations between earlier and later mental disorders. The 17 predictor disorders were treated as time-varying covariates in a discrete-time (person-year) survival framework. Controls were also included for respondent age at interview, sex, person-year, and country. B, Schematic of the multivariate latent variable model. Only 3 observed lifetime time *t* internalizing disorders and externalizing disorders and only 3 disorders of each set at time $t+1$ are shown to simplify the presentation, but there were 10 observed lifetime internalizing and 8 observed externalizing disorders in the actual survival model. First onset of each of these 18 disorders between times *t* and $t+1$ was predicted by latent internalizing or latent externalizing variables at time $t+1$. These latent variables, in turn, were predicted by lifetime history of latent internalizing and externalizing variables as of time *t*. These time *t* latent variables, finally, were predicted by lifetime history of observed internalizing or externalizing variables as of time *t*. Estimation was performed using a 3-part iterative procedure. A total of 36 independent associations were estimated, 270 fewer than in the model for associations among observed disorders. As in the earlier observed variable model, the predictor disorders were treated as time-varying covariates in a discrete-time (person-year) survival framework, and controls were included for respondent age at interview, sex, person-year, and country. e indicates externalizing; i, internalizing. The Greek letters δ and ε represent measurement errors in observed i and e variables, respectively. Lowercase letters signify measured variables; and uppercase, latent variables.

coefficients in the 3 parts of the model (time *t* observed variables predicting time *t* latent variables, time *t* latent variables predicting time $t+1$ latent variables, and time $t+1$ latent variables predicting time $t+1$ observed variables), each time holding constant the coefficients in the other 2 parts of the model to their values in the previous iteration, until estimates converged.

Once estimated, a likelihood-ratio χ^2 test was used to compare the fit of the latent variable model and the observed variable model with 270 (306–36) degrees of freedom. As described in the "Results" section, the latent variable model provided a better fit. We also investigated whether any of the 306 pairwise associations remained significant after controlling for the latent variables. Simple pairwise tests were inappropriate here because separate .05-level tests would generate more than a dozen false-positive results of 306 tests. The Bonferroni method and its extensions deal with this problem,[42] but these are low-power tests that make it difficult to detect all but the largest true associations.[43] We consequently used an internal subsampling strategy to pinpoint pairwise associations for

Table 2. Prevalence and Rotated (Promax) Factor Pattern of Lifetime Disorders Separately in Developed and Developing World Mental Health Countries[a]

Disorder	Estimated Lifetime Prevalence (SD), %			Standardized Regression Coefficient, Survey Part					
				Developed Countries		Developing Countries		Total	
	Developed Countries	Developing Countries	Total	1	2	1	2	1	2
Internalizing disorders									
Agoraphobia[b]	1.8 (13.0)	1.0 (9.9)	1.3 (11.0)	0.87	–0.11	0.74	–0.16	0.82	–0.14
Bipolar I-II disorder	4.4 (22.9)	2.0 (15.1)	2.8 (18.3)	0.37	0.31	0.54	0.20	0.46	0.27
Generalized anxiety disorder	4.9 (22.0)	1.4 (12.5)	2.6 (16.8)	0.67	0.04	0.72	–0.02	0.69	0.05
Major depressive episode/dysthymia	17.5 (40.9)	9.4 (33.1)	12.0 (36.5)	0.72	0.07	0.69	0.09	0.71	0.09
Obsessive-compulsive disorder	6.9 (29.7)	5.8 (32.6)	6.2 (31.7)	0.51	0.12	0.71	–0.17	0.63	–0.04
Panic disorder[c]	3.4 (16.6)	0.7 (8.0)	1.6 (11.8)	0.65	0.10	0.51	0.17	0.60	0.17
Posttraumatic stress disorder	4.4 (25.4)	1.6 (14.8)	2.6 (19.5)	0.57	0.18	0.43	0.18	0.52	0.21
Separation anxiety disorder	5.8 (25.3)	5.5 (24.2)	5.6 (24.6)	0.54	0.20	0.47	0.14	0.50	0.15
Social phobia	7.7 (30.4)	2.6 (18.5)	4.3 (23.7)	0.72	0.09	0.74	–0.04	0.71	0.09
Specific phobia	10.4 (35.4)	7.1 (32.3)	8.2 (33.3)	0.75	–0.13	0.78	–0.16	0.79	–0.16
Externalizing disorders									
Attention-deficit disorder	3.4 (23.5)	0.8 (9.5)	1.6 (15.8)	0.30	0.51	0.36	0.57	0.31	0.55
Hyperactivity disorder	2.7 (19.7)	0.6 (8.4)	1.3 (13.7)	0.19	0.58	0.32	0.60	0.22	0.61
Conduct disorder (overt)[d]	1.6 (15.3)	0.8 (9.2)	1.1 (11.6)	–0.09	0.94	–0.03	0.90	–0.08	0.93
Conduct disorder (covert)[e]	4.5 (31.1)	1.8 (15.6)	2.7 (22.1)	–0.04	0.90	0.05	0.84	–0.01	0.87
Intermittent explosive disorder	6.9 (32.5)	4.2 (28.1)	5.1 (29.9)	0.15	0.61	0.48	0.30	0.29	0.47
Oppositional defiant disorder	4.9 (34.0)	3.3 (20.9)	3.9 (26.1)	0.10	0.80	–0.02	0.73	0.02	0.78
Alcohol abuse[f]	9.7 (42.3)	8.0 (34.7)	8.5 (37.5)	0.01	0.76	–0.14	0.63	–0.06	0.73
Drug abuse[e]	6.4 (31.3)	2.7 (21.0)	3.9 (25.0)	–0.06	0.79	–0.15	0.69	–0.08	0.77
No. of respondents[g]	7360	13 869	21 229						

[a] Results are based on principal axis factor analysis of tetrachoric correlation matrices estimated in person-year data sets. Disorders are defined by *DSM-IV* criteria and the Composite International Diagnostic Interview.
[b] Indicates with or without panic disorder.
[c] Indicates with or without agoraphobia.
[d] Includes, for example, bullying, fighting, and being physically cruel to people.
[e] Includes, for example, lying and shoplifting.
[f] Indicates with or without dependence.
[g] The numbers of person-years (every year of life of the respondents beginning at 4 years to the age at interview) are 214 738 (developed countries), 376 961 (developing countries), and 591 699 (total).

further investigation by estimating observed variable survival models controlling for the latent variables in subsets of person-years. Rather than use random subsamples, which would simply have produced patterns determined by the rules of random sampling, we focused on meaningfully different subsamples defined by 4 independent life course stages (childhood, ages 4-12 years; adolescence, ages 13-19 years; young adulthood, ages 20-29 years; and middle adulthood, ages 30-44 years) and considered a given pairwise association substantively significant only if it was statistically significant at the .05 level in the total sample and in at least 2 independent subsamples with consistent sign patterns and ORs (exponentiated survival coefficients) greater than or equal to 2.0 or less than or equal to 0.5. Because the WMH data are clustered and weighted, the design-based method of jackknife repeated replications[44] was used to calculate standard errors and assess statistical significance. A SAS macro was used for this purpose.[41]

RESULTS

EXPLORATORY FACTOR ANALYSIS

Exploratory factor analysis of the 18 lifetime *DSM-IV*/CIDI disorders was performed separately in developed and developing countries. Only 2 meaningful factors were found, with unrotated eigenvalues of 8.0 and 1.8 (in developed countries) and 6.6 and 2.3 (in developing countries). Promax-rotated factor loadings (standardized partial regression coefficients) showed that the factors correspond to internalizing and externalizing dimensions (**Table 2**). All the mood and anxiety disorders other than BPD loaded clearly on the internalizing factor (0.43-0.87 standardized regression coefficients). All the behavior and substance disorders other than IED loaded clearly on the externalizing factor (0.51-0.94 standardized regression coefficients). Bipolar disorder cross-loaded in developed countries (0.31-0.37) and IED in developing countries (0.30-0.48). However, country-level analyses found that BPD generally loaded more strongly on the internalizing factor and IED on the externalizing factor, leading us to classify them with these dimensions in further analyses. (Detailed results are not reported herein, but are available from the authors on request.) Separate factor analysis of only the internalizing disorders found no reliable secondary distinction between fear and other distress disorders (unrotated eigenvalues of 4.8 and 1.0 in developed countries and 4.3 and 1.3 in developing countries).

BIVARIATE AND MULTIVARIATE ASSOCIATIONS BETWEEN EARLIER AND LATER DISORDERS

As noted, we estimated 306 bivariate survival equations, each with the first onset of 1 disorder predicted by the prior

Table 3. Associations of Lifetime Disorders With Subsequent First Onset of Other Disorders Based on Bivariate and Multivariate Survival Models in the Total Sample[a]

	Distribution of ORs				
	Median (Range)	IQR	Positive, %	Positive and Significant, %	No. of ORs
Internalizing predicting internalizing					90
Bivariate	3.6 (1.2-10.4)	3.0-4.3	100.0	97.8	
Multivariate	1.6 (0.4-5.5)	1.1-2.0	87.8	58.9	
Externalizing predicting internalizing					80
Bivariate	3.2 (1.7-7.5)	2.6-3.7	100.0	98.8	
Multivariate	1.3 (0.5-3.2)	1.0-1.6	80.0	28.8	
Internalizing predicting externalizing					80
Bivariate	3.0 (0.4-10.3)	2.4-3.9	96.3	90.0	
Multivariate	1.3 (0.1-3.2)	0.9-1.6	70.0	33.8	
Externalizing predicting externalizing					56
Bivariate	5.5 (0.5-30.0)	3.3-8.2	94.5	92.7	
Multivariate	1.6 (0.2-13.4)	1.2-2.9	81.8	50.9	
Total					306
Bivariate	3.4 (0.4-30.0)	2.7-4.3	98.0	95.1	
Multivariate	1.4 (0.1-13.4)	1.1-1.9	80.0	43.0	

Abbreviations: IQR, interquartile range; OR, odds ratio.
[a]First lifetime onset of each of 18 *DSM-IV*/Composite International Diagnostic Interview disorders was predicted by a single dummy variable for lifetime history of 1 of the other disorders (bivariate model) or 17 dummy variables for history of each of the 17 other disorders (multivariate model) in discrete-time (person-year) survival models. The predictor disorders and latent variables were treated as time-varying covariates. Controls were included for respondent age at interview, person-year, sex, and country. Data include 21 229 respondents.

occurrence of 1 of the other 17 disorders. Of the 306 survival coefficients, 98.0% were positive and 95.1% were also significant (**Table 3**). (Detailed results are not reported herein, but are available from the authors on request.) The median (interquartile range) ORs were 3.4 (2.7-4.3). None of the negative ORs was significant. Within-domain ORs were generally larger than between-domain ORs, with within-domain median ORs of 3.6 to 5.5 compared with between-domain medians of 3.0 to 3.2.

This largely positive pattern persisted in attenuated form in multivariate models, with 80.0% of ORs positive and 43.0% positive and statistically significant (Table 3). The median (1.4) and interquartile range (1.1-1.9) of ORs were considerably lower than in bivariate models because of strong intercorrelations among predictor disorders. Nine of the 306 multivariate ORs were negative and significant (GAD predicting agoraphobia and specific phobia; HD, PTSD, and CD1 predicting OCD; CD2 predicting GAD and PTSD; and alcohol abuse predicting ADD and HD). Of the within-domain ORs, 50.9% to 58.9% were positive and significant compared with 28.8% to 33.8% of between-domain ORs. The median OR was higher within (1.6) than between (1.3) domains.

MULTIVARIATE ASSOCIATIONS IN THE LATENT VARIABLE MODEL

The latent variable model fit the observed data better than the observed variable model, as indicated by a lower Bayesian information criterion[45] of 7514.3 (latent) vs 7530.0 (observed) and an insignificant improvement in likelihood-ratio χ^2 of the observed variable model ($\chi^2_{270}=107.8$; $P=.99$). Latent variable coefficients were quite stable, as indicated by the Pearson correlations of model coefficients across 4 samples (the total sample and the 3 subsamples of all developed countries, all developing countries, and all countries excluding the 4 with survey response rates of less than 60% [Belgium, France, Germany, and the Netherlands]) of 0.88 to 0.97. (Detailed results are not reported herein, but are available from the authors on request.)

As noted, the latent variables are actually weighted (by ORs of disorders predicting latent variables) composites of all predictor disorders. The assumption that a single weighted composite can represent the effects of all the predictor disorders on all outcomes is equivalent to assuming that the ratios of the ORs across predictors are constant across outcomes. The good fit of the latent variable model shows that this assumption is generally consistent with the data, which means that the predictive effects of these disorders on each other can plausibly be assumed to be mediated by common internalizing and externalizing pathways.

The metric of the time *t* latent variables was set by fixing the slope of the latent variable on the strongest time *t* predictor to 1.0 and scaling other slopes relative to that value (**Table 4**). Within the internalizing domain, specific phobia was by far the most powerful predictor (1.00 by definition), followed by OCD (0.62) and other phobias (0.46-0.48) (Table 4). At the other extreme, GAD and panic disorder were insignificant predictors. The remaining internalizing disorders had ORs of intermediate strength (0.18-0.44). Within the externalizing domain, HD (1.00) and ODD (0.97) were the most powerful predictors. Alcohol and other drug abuse were insignificant, and the remaining externalizing disorders had ORs in the range of 0.43 to 0.77.

The ORs for the disorders as outcomes were much more consistent than for the disorders as predictors, with ranges of 0.68 to 1.00 (internalizing) and 0.44 to 1.00

Table 4. Parameter Estimates for Associations Between Observed Disorders and Latent Variables in the Latent Variable Model[a]

Disorder	Estimate (SE)	
	Time *t* Disorders Predicting Time *t* Latent Variables	Time *t*+1 Latent Variables Predicting Time *t*+1 First Onset of Disorders
Internalizing		
Agoraphobia	0.48 (0.09)[b]	1.00 (0.09)[b]
Bipolar I/II disorder	0.18 (0.08)[b]	0.85 (0.05)[b]
Generalized anxiety disorder	0.02 (0.07)	0.72 (0.05)[b]
Major depressive episode	0.29 (0.06)[b]	0.68 (0.04)[b]
Obsessive-compulsive disorder	0.62 (0.07)[b]	0.87 (0.06)[b]
Panic disorder	–0.02 (0.10)	0.82 (0.05)[b]
Posttraumatic stress disorder	0.21 (0.08)[b]	0.68 (0.05)[b]
Separation anxiety disorder	0.44 (0.06)[b]	0.74 (0.05)[b]
Social phobia	0.46 (0.05)[b]	0.97 (0.05)[b]
Specific phobia	1.00 (0.09)[b]	0.86 (0.10)[b]
Externalizing		
Attention-deficit disorder	0.77 (0.24)[b]	1.00 (0.31)[b]
Hyperactivity disorder	1.00 (0.23)[b]	0.95 (0.16)[b]
Conduct disorder (overt)	0.43 (0.18)[b]	0.74 (0.16)[b]
Conduct disorder (covert)	0.57 (0.23)[b]	0.78 (0.16)[b]
Intermittent explosive disorder	0.77 (0.15)[b]	0.52 (0.08)[b]
Oppositional defiant disorder	0.97 (0.18)[b]	0.69 (0.15)[b]
Alcohol abuse disorder	–0.53 (0.35)	0.44 (0.08)[b]
Drug abuse disorder	0.51 (0.31)	0.38 (0.13)[b]

[a] Based on an iteratively estimated pooled discrete-time (person-year) survival model with 17 dummy variables for history of each other disorder predicting subsequent first onset of each of the 18 disorders, assuming the existence of latent internalizing and externalizing disorders that explain the direct effects of the observed predictor disorders on the outcome disorders. The predictor disorders and latent variables were treated as time-varying covariates. Controls were included for respondent age at interview, person-year, sex, and country. Data include 21 229 respondents.

[b] Significant at the .05 level, 2-sided test.

(externalizing). Agoraphobia and social phobia were the most strongly predicted internalizing disorders, whereas ADD and HD were the most strongly predicted externalizing disorders. The relative importance of internalizing and externalizing disorders predicting each other was estimated in the set of 4 ORs between the latent variables at times *t* and *t* + 1 (**Table 5**). Weighted (by relative prevalence of disorders) within-domain ORs (1.6 for internalizing; 1.4 for externalizing) were higher than between-domain ORs (1.3 for time *t* internalizing predicting time *t* + 1 externalizing; 1.1 for time *t* externalizing predicting time *t* + 1 internalizing), but between-domain ORs were nonetheless statistically significant.

RESIDUAL ASSOCIATIONS NOT EXPLAINED BY THE LATENT VARIABLE MODEL

Only 13 of the 306 residual pairwise time-lagged associations between observed disorders passed our test of statistical significance. Nine of these were positive. Four involved within-disorder reciprocal ORs between CD1 and CD2 (3.2-4.8) and between ADD and HD (4.0-19.4). Two others involved asymmetrical associations between well-known disorder pairs (panic predicting agoraphobia [2.0-2.22] and depression predicting GAD [2.0-6.0], although the latter association was limited to child-adolescent onset). Two others might reflect diagnostic confusions, with agoraphobia predicting specific phobia (2.2-4.8) and HD (but, importantly, not ADD) predicting BPD (1.9-3.9). The final significant positive association was for IED predicting OCD (1.5-4.0). The 4 significant negative residual associations included PTSD predicting OCD (0.4-0.7), CD2 predicting BPD (0.2-0.5) and PTSD (0.2-0.4), and IED (0.5-0.6) predicting drug abuse.

COMMENT

Six limitations of this study are noteworthy. First, diagnoses were based on fully structured lay interviews. These typically produce more reliable (ie, reproducible across multiple interviewers) diagnoses than semistructured clinical interviews,[46] and their prevalence estimates typically correspond well with those based on clinical interviews.[47] However, fully structured interviews, unlike semistructured clinical interviews, are unable to clarify symptom responses or check questions across disorders to facilitate differential diagnosis, potentially leading to inflated estimates of comorbidity.

Second, disorders were assessed dichotomously rather than dimensionally, presumably reducing our ability to detect subtle aspects of structure in the data. This might help explain why we did not detect higher-order subfactors in the 2-factor exploratory factor analysis model.

Third, data were combined across countries with very different cultures and across surveys with very different response rates (which could have introduced variation in sample selection bias), different rates of sample exclusion (due to cross-national differences in rates of suicide, homelessness, and institutionalization), and different languages in which interviews were administered. Although every effort was made to make the translations as comparable as possible,[34] residual variation in meaning almost certainly contributed to cross-national variation in results.

Fourth, lifetime diagnoses were based on retrospective reports rather than prospective assessments, probably leading to recall bias that underestimated prevalence[48] and distorted age-at-onset estimates[49] despite the use of special memory-priming methods.[38] Bias in model coefficients might have varied across disorders as a function of age at onset and/or recency. Given the importance of this potential bias, it is noteworthy that the onset distributions based on these retrospective data are quite consistent with those based on prospective studies and studies performed at separate life course stages.[50] In addition, model coefficients in subsamples defined by life course stage are very consistent, suggesting that variation in recall across the sample age range does not influence results in any important way.

Fifth, models were based on the simplifying assumptions that the time-lagged associations among mental disorders are constant across countries and sex, stable across the life course, and unrelated to age at onset or time since onset of the predictor disorders. Preliminary analyses showed that these assumptions are a reasonable first approximation, but the investigation of these specifications needs to be a focus of ongoing WMH analysis.

Sixth, we did not take history of treatment into consideration even though early treatment, which varies in frequency across countries,[51] might interrupt the progression of comorbidity and thereby distort estimates of predictive associations.

In the context of these limitations, our finding of a 2-factor internalizing-externalizing structure among WMH disorders is consistent with previous research[4-9] but does not support the distinction in some previous studies between distress (eg, depression, GAD, and PTSD) and fear (eg, panic and phobias) disorders. As noted in the introduction, others also failed to find a distinction between distress and fear disorders.[16,52] This less-differentiated structure in the WMH data might be due to our focus on lifetime disorders, whereas 12-month disorders were the focus of most studies that distinguished distress and fear disorders.

Our finding of significant time-lagged associations across virtually all pairs of the disorders considered herein is broadly consistent with evidence of associations between earlier and later disorders in previous longitudinal studies,[18-23] although most previous studies focused on prevalent cases, whereas we studied first onsets. We found, again consistent with previous studies, stronger and more consistent time-lagged associations within than between the internalizing and externalizing domains. However, again as in previous studies, we also found significant between-domain time-lagged associations.[22,23]

Our analysis went beyond previous studies to investigate the role of latent variables in the development of comorbidity. We showed that most of the 306 pairwise time-lagged associations among the 18 disorders considered herein can be explained by a model that assumes the existence of mediating latent internalizing and externalizing variables. This finding extends previous cross-cultural work on the structure of comorbidity.[53] The fact that the predictive associations across this large number of disorders are mediated by 2 higher-order variables makes the internalizing and externalizing spectrum dimensions compelling targets for inquiry aimed at reducing the burden of mental disorder around the world by interrupting the processes leading to the onset of comorbidity.

Table 5. Parameter Estimates for Associations Among Latent Variables in the Latent Variable Model[a]

Time 1 Predictor Group	Time 2 Dependent Group, OR (95% CI)[b]	
	Internalizing	Externalizing
Internalizing	1.6 (1.5-1.6)	1.3 (1.2-1.3)
Externalizing	1.1 (1.1-1.2)	1.4 (1.3-1.4)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Data include 21 229 respondents.
[b] All comparisons were significant at the .05 level, 2-sided test.

Specific phobia and OCD stood out as the most important internalizing predictors and HD and ODD as the most important externalizing predictors. The time-lagged associations involving these 4 predictors were largely mediated by the latent variables, with only 2 of the 13 significant residual associations involving these 4 strongest predictors (HD predicting ADD and BPD). Both of these were positive, showing that the comparatively high ORs of these 4 predictor disorders are relatively constant across the range of WMH outcomes. Although it is unclear why specific phobia and OCD should be the most important predictors among the internalizing disorders or HD and ODD among the externalizing disorders, the fact that all 4 are typically early-onset disorders[50] means they might be useful markers of youth at high risk for progression to later disorders. Even this possibility requires further analysis, however, because we did not investigate nonproportional hazards that might include differential predictive associations related to age at onset or time since onset. These more in-depth analyses go beyond the scope of this first report but will be pursued in ongoing WMH analyses.

Our finding of 13 significant residual associations shows that the latent variables do not explain all the comorbidity among the disorders considered. The 4 negative residual associations are most plausibly interpreted as suggesting the existence of more differentiated dimensions underlying internalizing and externalizing disorders. The negative association of IED with subsequent drug abuse, for example, could be due to externalizing disorders being made up of multiple dimensions, 1 or more of which is significantly more strongly related to drug abuse than to IED. Evidence consistent with this possibility exists in the literature.[54-56] The negative residual association of CD2 (overt CD) with subsequent PTSD, in comparison, might be related to the findings that blunted psychophysiological and emotional reactivity to fear stimuli are predictors of CD,[57,58] whereas heightened physiological reactivity to trauma-related stress cues is a predictor of PTSD.[59,60] These observations suggest that a more differentiated latent variable model that includes internalizing and externalizing subdimensions might explain the significant negative associations found herein in the less differentiated WMH latent variable model.

The positive residual associations in the WMH data, in comparison, are most plausibly interpreted as disor-

der subtypes rather than comorbidities, including the reciprocal associations between CD1 (covert CD) and CD2 (overt CD) and between ADD and HD, or as a severity marker in the association between panic disorder and subsequent agoraphobia. At least 1 other association, between agoraphobia and subsequent specific phobia, could be due to diagnostic confusion in the CIDI. The same kind of confusion might account at least in part for the positive association between HD and subsequent BPD because differentiation between these 2 disorders can be difficult, especially within the constraints of a fully structured diagnostic interview,[61,62] although a number of common neurobiological correlates have also been found for HD and BPD,[63,64] arguing that ADHD might be a risk marker of BPD. The WMH finding that this association is specific to HD and does not apply to ADD has not, to our knowledge, been investigated previously.

It is important to caution that these few unique, significant residual pairwise associations should be treated as no more than preliminary owing to the problem of multiple testing and the limitations noted at the beginning of this section. Replication in other data sets, most importantly prospective data sets, is needed before these associations should be considered reliable. Furthermore, even if they are subsequently found to be reliable, their existence should not deflect attention from our main finding that the consistently significant comorbidities found among the 306 disorder pairs considered herein are likely due to common underlying processes that should be a major focus of future research on the development of comorbidity. One important implication of this finding is that future research on specific pairwise comorbid associations needs to guard against interpreting results as unique without first demonstrating, as we did herein, that they are specific rather than mere realizations of larger processes involving all internalizing and/or externalizing disorders. The fact that we found only 2 factors, finally, does not mean that only 2 underlying processes are at work because multiple processes could underlie each factor, and these diverse processes need to be studied to enrich our understanding of the causal influences leading to the higher-order structure found herein.

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